



1500 Waukegan road
McGaw Park, IL 60085
847-473-1500

11/18/04

Mr. Gary Buehler
Food and Drug Administration
Office of Generic Drugs
Document Mail Center (HFD-600)
7500 Standish Place
Rockville, MD 20855

Dear Mr. Buehler:

Cardinal Health is submitting this Suitability Petition to the FDA requesting permission to file an ANDA for a preoperative prep containing a chlorhexidine gluconate (CHG) / isopropol alcohol (IPA) solution with tint. More specifically, the intent of this petition is to address the change in applicator volume from 10.5 ml to 26 ml.

A. Action Requested:

As indicated above, Cardinal Health proposes to file an ANDA based upon the reference listed drug (RLD) ChloraPrep® One-Step chlorhexidine gluconate 2% (w/v) and isopropyl alcohol 70% (v/v) antiseptic patient preoperative skin preparation (10.5 mL) (hereinafter referred to as ChloraPrep) manufactured by Medi-Flex, Inc., (NDA 20-832) and the recent ANDA submission by Cardinal Health for a similar product (ANDA 77-271). The marketing exclusivity of the reference listed drug expired July 14, 2003. The specific intent of this petition is to request approval for a change in applicator volume from 10.5 ml to 26 ml.

B. Statement of Grounds:

The active ingredients in the proposed Cardinal Health drug product, CHG and IPA, are the same as those of the reference listed drug approved in NDA No. 20-832. The dosage form and strength of the proposed product are also the same as those of the reference listed drug approved in NDA No. 20-832. The inactive ingredients in Cardinal Health's Prevail-CHG and ChloraPrep are presented in the following table.

Inactive Ingredients in Prevail-CHG and ChloraPrep	
Prevail-CHG	ChloraPrep ^a
Purified Water, USP	Purified Water, USP
FD&C Red No. 40	
^a Inactive ingredients listed on ChloraPrep labeling are provided	

There is considerable commercial experience with one-step preoperative prep products containing alcohol. As summarized in the following table, the widespread use of Povidone Iodine-plus-alcohol based products, such as 3M's Dura-Prep (26 ml) and Cardinal Health's Prevail (59 ml) and Prevail-FX (40 ml) represent an estimated 70% of the entire preoperative prepping market..

2004P-0528

CPI

Currently Marketed Patient Preoperative Prepping Solutions Containing Alcohol		
DuraPrep^R, 26 ml	Iodophor and IPA (0.7% Available Iodine and 74% IPA w/w)	6,000,000 units est. sold annually.
Cardinal Large Applicators (Prevail^R, 59 ml; Prevail-Fx, 40 ml)	Povidone Iodine USP and Alcohol (Prevail: 0.5% Available Iodine and 62% v/v Ethanol) (Prevail-Fx: .83% Available Iodine and 72.5% IPA w/w)	1,000,000 units est. sold annually.
ChloraPrep^R, 10.5 ml	Chlorhexidine Gluconate and IPA (2% CHG w/v and 70% IPA v/v)	1,500,000 units est. sold annually.

It is speculated that the reason for the relatively high use of products containing more than 10.5 ml of solution is that a majority of surgical procedures require larger volumes of solution to prep the area of concern. The surface area of a typical human body is approximately 2800 square inches, (referencing Cornell University website <http://www-users.med.cornell.edu/~spon/picu/calc/bsacalc.htm>). The 10.5 ml applicator covers an area of about 8.4 square inches. It is evident that preparing a patient for typical procedures such as laparoscopies would normally require more than a single applicator. Through clinical observation and discussion with practitioners, it has been determined that a full-body prep commonly uses 80 ml of antimicrobial solution in the preparation of skin for surgery. Eight (8) separate containers of the 10.5 ml RLD would have to be opened in this case, significantly increasing the time for prepping as well as negatively impacting the cost of the procedure. Using Cardinal Health products as a case study, the packaging and sterilization costs are approximately half of the total product cost. In addition, it would take practitioners extra time and effort to obtain and open the units without improving patient or clinician safety. The proposed Cardinal Health product has been developed in consideration of cost and convenience.

Cardinal is aware that there is concern with OR fires associated with prepping solutions containing a high percentage of alcohol. This concern, as well as customer safety, was taken into consideration during the design of the Cardinal applicator. With many products on the market, notably DuraPrep and ChloraPrep, the container holding the fluid is a glass ampoule, which is broken during applicator activation. Once broken, there is no means of controlling fluid flow through the sponge of the applicator and onto the surgical site. With the Cardinal Health applicator system, the container for the fluid is an HDPE bottle. Once the foil seal on the neck of the bottle is punctured, fluid can be expelled through the neck of the bottle by squeezing or, conversely, fluid flow will be slowed significantly by merely holding the bottle without squeezing. This applicator is the same as that of Cardinal's currently sold prep products, i.e., Prevail and Prevail-Fx.

The proposed prep contains 70% isopropyl alcohol, which provides fast and broad-spectrum antimicrobial kill. Additionally, this alcohol allows for quick dry time (2-3 minutes). Combined with CHG, this system yields an extremely fast-acting, persistent preoperative skin preparation.

Based on investigations, published figures, and searches of the U.S. Food and Drug Administration's (FDA) medical device reporting databases, ECRI estimates that 100 surgical fires per year occur in the United States each year (Risk Management Reporter, Oct 2003). In conversations with Mark E. Bruley (ECRI Vice President, Accident and Forensic Investigation), roughly 5-15% of these surgical fires are attributed to alcohol-based preps.

It has been well established that for a fire to occur, an ignition source, fuel and oxidizer must be present. Alcohol and alcohol-based preps are flammable until all liquid has evaporated (Health Devices, November 2003). Once dry, the solution is no longer flammable. It is important to note that the OR fires are easily prevented through education and training of proper application methods and dry times.

In conjunction with the concern of excess fluid being applied to the area being prepped, there is also a concern that hospital linens or drapes will become saturated and will not be removed or replaced prior to coming in contact with an ignition source. The proposed product label clearly warns of the concerns with use of a flammable solution. It also provides instructions on removal of soaked materials and advises users to allow for sufficient drying of solutions prior to surgery. Please refer to correspondence between the 3M Corporation and the FDA, docket Management Branch (HFA-305), dated June 15, 1995 Docket No. 75N-183H, where a detailed review of cause and corrective action, notably awareness and training of the professional OR staff.

In conclusion, Cardinal Health's proposed prep product has been developed to address cost, convenience and the safety concerns of the OR staff. It is our opinion that the proposed Cardinal product with a change in packaging size to 26 ml as compared to the 10.5 ml packaging size of the RLD is suitable to be filed as an ANDA.

C. Environmental Impact Statement:

By providing a single applicator containing 26 mls of solution, the end user is cutting in half the amount of waste generated during patient preoperative prepping with use of the RLD.

D. Economic Impact Statement:

Not required at this time.

E. Certification:

The undersigned certified that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.



Michael L. Groesbeck

Vice President, Quality Operations, Infection
Infection Prevention, Cardinal Health

1500 Waukegan Rd., Bldg. WM
McGaw Park, IL 60085
(847) 785-3267

Attachments:

Label copy for Prevail-CHG2: Bottle, Pouch, Case Label
Label copy for ChloroPrep^a Bottle, Pouch, Dispenser



Cat. 4VAIL-CHG2

NDC 63517-015-26

Prevail-CHG™

One Step Topical Preoperative Prep Solution and Applicator

Contains Chlorhexidine Gluconate 2% (w/v) and Isopropyl Alcohol 70% (v/v)

Each bottle contains 26 mL

Single application provides fast-acting, broad-spectrum, persistent antimicrobial activity.

Sterile

For Single External Use Only

Contents

One (1) 26 mL Applicator (urethane sponge)

Contents in unopened, undamaged package are sterile

Prevail-CHG™



Drug Facts	
Active ingredient Chlorhexidine gluconate 2% (w/v) Isopropyl alcohol 70% (v/v).	Purpose Antiseptic Antiseptic
Use for preparation of the patient's skin prior to surgery	
Warnings ■ flammable , keep away from fire or flame. ■ do not drape or use ignition source until dry. (e.g. electrocautery/laser) ■ for external use only. ■ do not allow to pool. ■ remove all solution soaked materials. ■ if prep accidentally drips into hair, allow to dry completely. Do not use ■ on children less than 2 months of age because of the potential for excessive skin irritation and increased drug absorption. ■ on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol. ■ for lumbar puncture or in contact with the meninges. ■ on open skin wounds or as a general skin cleanser. When using this product keep out of eyes, ears, and mouth. May cause serious or permanent injury if permitted to enter and remain. If contact occurs, rinse with cold water right away and contact a physician. Stop use and ask a doctor if irritation, sensitization, or allergic reaction occurs. These may be signs of a serious condition. Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.	
Directions ■ peel pouch, exposing components. ■ remove applicator from pouch. ■ hold bottle and neck of the applicator cap. ■ turn bottle in direction of arrow and push applicator down onto bottle until a snap is heard. ■ invert bottle and squeeze to dispense solution. ■ dry surgical sites (such as abdomen or arm): use repeated back-and-forth strokes of the sponge for approximately 30 seconds. Completely wet the treatment area with antiseptic. Allow the area to air dry for approximately 30 seconds. Do not blot or wipe away. ■ moist surgical sites (such as the inguinal fold): Use repeated back-and-forth strokes of the sponge for approximately 2 minutes. Completely wet the treatment area with antiseptic. Allow the area to air dry for approximately one (1) minute. Do not blot or wipe away. ■ maximum treatment area for one applicator is approximately 734 cm ² (17 in. x 17 in.). Discard the applicator after a single use.	
Other information ■ store between 20–25°C (68–77°F) ■ avoid freezing and excessive heat above 40°C (above 104°F)	
Inactive ingredients ■ FD&C Red No. 40 and purified water, USP	
Questions? 800-964-6227 (Monday to Friday 8 AM – 5 PM)	

Cardinal Health
McGaw Park, IL 60085 USA
30-XXXX



(01) 0 0380470 17978 0



MK090411
Medivac-Prep-Thermal B.U.
McGaw Park, IL
M. Kraemer
9/30/04
30-XXXX

Proofed by: _____ Date: _____
Dimensions checked: _____ Copy checked: _____

Cat 4VAIL-CHG2 N 63517-015-26

Prevail-CHG¹⁰²
One Step Topical
Preoperative Prep
Solution and Applicator

Contains Chlorhexidine Gluconate
2% (w/v) and Isopropyl Alcohol
70% (v/v)

For Single External Use Only

Warning: Solution is flammable
until dry.

Contains 26 mL

Cardinal Health
McGaw Park, IL 60085 USA
37-XXXXX



MK090413

Medivac-Prep-Thermal B.U.

McGaw Park, IL

M. Kraemer

9/30/04

37-XXXXX

Proofed by: _____ Date: _____

Dimensions checked: _____ Copy checked: _____

Cat. 4VAIL-CHG2	NDC 63517-015-26	Qty. 20
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Prevail-CHG™
One Step Topical Preoperative Prep
Solution and Applicator

Contains Chlorhexidine Gluconate 2% (w/v) and
Isopropyl Alcohol 70% (v/v)

Sterile

Lot No.

Exp.

CONSUMER COMMODITY

ORM-D

Warning: Solution is
flammable until dry.



Store at 20–25°C (68–77°F). Avoid freezing and
excessive heat above 40°C (above 104°F).

Each Bottle Contains 26 mL

U.S. components assembled in Mexico

Cardinal Health
McGaw Park, IL 60085 USA

37-XXXXX



(01) 5 0380470 17978 5


Cardinal Health

MK090412
Medivac-Prep-Thermal B.U.
McGaw Park, IL
M. Kraemer
9/30/04
37-XXXXX

Proofed by: _____ Date: _____

Dimensions checked: _____ Copy checked: _____



Cat. No. 260700 NDC #054365-400-04 DIN#02160757

Chloraprep® One-Step

Chlorhexidine Gluconate 2% w/v and Isopropyl Alcohol 70% v/v
Patient Preoperative Skin Preparation • 10.5mL Applicator

**WARNING. FLAMMABLE. KEEP AWAY FROM FIRE OR FLAME.
DO NOT USE WITH ELECTROCAUTERY PROCEDURES.**

Drug Facts

Active ingredients	Purpose
Chlorhexidine gluconate 2% w/v	Antiseptic
Isopropyl alcohol 70% v/v	Antiseptic

Use for the preparation of the patient's skin prior to surgery

Warnings

For external use only

Flammable: Keep away from fire or flame. Do not use with electrocautery procedures.

Do not use

- in children less than 2 months of age because of the potential for excessive skin irritation and increased drug absorption
- on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol
- for lumbar puncture or in contact with the meninges
- on open skin wounds or as a general skin cleanser

When using this product keep out of eyes, ears, and mouth. May cause serious or permanent injury if permitted to enter and remain. If contact occurs, rinse with cold water right away and contact a physician.

Stop use and ask a doctor if irritation, sensitization, or allergic reaction occurs. These may be signs of a serious condition.

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions

- pinch the wings on the applicator to break the ampule and release the antiseptic. Do not touch the sponge. Wet the sponge by repeatedly pressing and releasing the sponge against the treatment area until liquid is visible on the skin.
- **dry surgical sites** (such as abdomen or arm): Use repeated back-and-forth strokes of the sponge for approximately **30 seconds**. Completely wet the treatment area with antiseptic. Allow the area to air dry for approximately 30 seconds. Do not blot or wipe away.
- **moist surgical sites** (such as the inguinal fold): Use repeated back-and-forth strokes of the sponge for approximately **2 minutes**. Completely wet the treatment area with antiseptic. Allow the area to air dry for approximately one (1) minute. Do not blot or wipe away.
- maximal treatment area for one applicator is approximately 457 cm² (approximately 8.4 x 8.4 inches). Discard the applicator after a single use.

Other information ■ store between 20-25°C (68-77°F)
■ avoid freezing and excessive heat above 40°C (104°F)

Inactive ingredients ■ USP purified water

Questions? Call 1-800-523-0502 (8 a.m.-5 p.m. CST)

Single Use
Applicator is **sterile** if package is intact

Lot No:

Exp. Date:



Chloraprep® 10.5-ml Applicator
2% (w/v) Chlorhexidine Gluconate
and 70% (v/v) Isopropyl Alcohol
Lot No. 405060 Exp. Date 04/06
Medi-Flex, Inc. Leawood, KS 66211

Part No: 6-824248
Rev. Date: 2/17/03



ChloroPrep® One-Step
10.5-mL Applicators • 25 qty.

Store at room temperature 20–25 °C (68–77 °F)
Avoid freezing and excessive heat above 40 °C (104 °F)

Cat. No. 260700 ND

Chloro

Chlorhexidine Gluc
Antiseptic Patient

ChloroPrep® One
persistent anti
number of micr

10.5-mL Applicator
Single Use

Applicator is sterile

Contents: 1 Each Spo
Quantity: 1 Box, 25 Ea

Store at room temper
Avoid freezing and ex

Part No: 6-824248
Rev. Date: 2/17/03



Chloraprep® One-Step
Applicators • 25 qty.

temperature 20–25 °C (68–77 °F)
and excessive heat above 40 °C (104 °F)

Cat. No. 260700 NDC #054365-400-0

Chloraprep

**Chlorhexidine Gluconate 2% (w/v)
Antiseptic Patient Preoperative Solution**

**Chloraprep® One-Step is a fast-acting,
persistent antiseptic that significantly reduces the
number of microorganisms on the skin.**

10.5-mL Applicator

Single Use

Applicator is *sterile* if package is intact

**Contents: 1 Each Sponge, Latex Free
Quantity: 1 Box, 25 Each/Box**

**Store at room temperature 20–25 °C (68–77 °F)
Avoid freezing and excessive heat above 40 °C (104 °F)**

00-04 DIN#02160757

ep[®] One-Step

w/v) and Isopropyl Alcohol 70% (v/v)
ive Skin Preparation

a fast-acting, broad spectrum,
at significantly reduces the
ms on intact skin.



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ChloraPrep® One-Step

10.5-mL Applicators • 25 qty.

Store at room temperature 20–25 °C (68–77 °F)
Avoid freezing and excessive heat above 40 °C (104 °F)



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Lot No: 405060

Exp. Date:

04-06

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Chlor

Chlorhexidine
Patient Prep

Drug Facts

Active ingredients
Chlorhexidine gluconate 2% w
Isopropyl alcohol 70% v/v

Use

■ for the preparation of the pr

Warnings

For external use only

Flammable: Keep away f

Do not use

- in children less than 2 mor
- on patients with known alle
- for lumbar puncture or in c
- on open skin wounds or as

When using this product

- keep out of eyes, ears, an

Stop use and ask a doc

- irritation, sensitization, or

Keep out of reach of ch

Directions

- pinch the wings on the ap
- Wet the sponge by repea
- **dry surgical sites** (su
- Completely wet the treatn
- **moist surgical sites**
- Completely wet the treatr
- maximal treatment area f

Other information

- store between 20–25 °C

Inactive ingredie

Questions? Call 1-8



is a fast-acting, broad spectrum,
that significantly reduces the
risk of surgical site infection.

Active Skin Preparation
(w/v) and Isopropyl Alcohol 70% (v/v)

ep one-step®

5-400-04 DIN#02160757

ChloraPrep® One-Step

Chlorhexidine Gluconate 2% w/v and Isopropyl Alcohol 70% v/v
Patient Preoperative Skin Preparation • 10.5-mL

DI-FLEX®

One-Step
Containers • 25 qty.

Store at 20–25 °C (68–77 °F)
Do not expose to heat above 40 °C (104 °F)



7002B*

04 06

Date:

Drug Facts

Active ingredients

Chlorhexidine gluconate 2% w/v
Isopropyl alcohol 70% v/v

Use

- for the preparation of the patient's skin prior to surgery

Warnings

For external use only

Flammable: Keep away from fire or flame. Do not use with electrocautery procedures

Do not use

- in children less than 2 months of age because of the potential for excessive skin irritation and increased drug absorption
- on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol
- for lumbar puncture or in contact with the meninges
- on open skin wounds or as a general skin cleanser

When using this product

- keep out of eyes, ears, and mouth May cause serious or permanent injury if permitted to enter and remain If contact occurs, flush thoroughly with water

Stop use and ask a doctor if

- irritation, sensitization, or allergic reaction occurs These may be signs of a serious condition

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away

Directions

- pinch the wings on the applicator to break the ampule and release the antiseptic Do not touch the sponge
- Use the sponge by repeatedly pressing and releasing the sponge against the treatment area until liquid is visible on the skin
- **dry surgical sites** (such as abdomen or arm) Use repeated back-and-forth strokes of the sponge for approximately **30 seconds** Completely wet the treatment area with antiseptic Allow the area to air dry for approximately 30 seconds Do not blot or wipe
- **moist surgical sites** (such as the inguinal fold) Use repeated back-and-forth strokes of the sponge for approximately **2 minutes** Completely wet the treatment area with antiseptic Allow the area to air dry for approximately one (1) minute Do not blot or wipe
- maximal treatment area for one applicator is approximately 457 cm² (approximately 8.4 x 8.4 inches) Discard the applicator after use

Other information

- store between 20–25 °C (68–77 °F) ■ avoid freezing and excessive heat above 40 °C (104 °F)

Inactive ingredients ■ USP purified water

Questions? Call 1-800-523-0502 (8 a.m.–5 p.m. CST)

Chloraprep® One-Step is a fast-acting, persistent antiseptic that significantly reduces the number of microorganisms on the skin. Chlorhexidine gluconate 2% (w/v) and Isopropyl Alcohol 70% (v/v).

Chloraprep

Cat. No. 260700 NDC #054365-400-04

One-Step

Chlorhexidine gluconate 2% (w/v) and Isopropyl Alcohol 70% v/v
 Application • 10.5-mL Applicator

Purpose
 Antiseptic
 Antiseptic

Increased drug absorption

After use, wash hands thoroughly. If contact occurs, rinse with cold water right away and contact a physician.

Center right away

Wipe the sponge until liquid is visible on the skin. Use the sponge for approximately **30 seconds** (30 seconds). Do not blot or wipe away the sponge for approximately **2 minutes** (2 minutes). Do not blot or wipe away the sponge (1 minute). Do not blot or wipe away the sponge (1 minute). Discard the applicator after a single use.

